REMARKS

Reconsideration of this application is respectfully requested. In view of the foregoing amendment, claims 1 to 8, 15 and 56 to 58 are pending in the application, with claim 1 being an independent claim. Claims 1, 5 and 57 are sought to be amended. Support for the amendments to claim 1 and 5 can be found in the specification as filed, e.g., at page 9, lines 17 to 22 and lines 27 to 31 and further basis for amended claim 5 can be found on page 13, lines 1 to 9. The subject matter of new claim 58 is supported by the disclosure content of the application as filed, for example at page 12, lines 20 to 28 and the Examples, e.g. at page 40, lines 2 to 3. The objections and rejections are addressed in order below.

1. Priority

Applicants are submitting herewith a Supplemental Declaration that addresses the issues noted by the Examiner.

2. Specification

As stated by the Examiner in section 5 on page 3 of the Office Action, the brief description of the drawings should be amended to reference Figure 6G. Therefore, please find enclosed an amended page 7, wherein reference to Figure 6G is made. Basis for this amendment can be found in the application as filed, e.g. in Example 2 at page 46, line 33 bridging to page 47, line 1.

3. Claim Objections

With respect to the claim objections in section 6 on page 4 of the Office Action, the objected amino acid reference, i.e. amino acid 158 - 457 in claim 57 has been deleted.

Regarding the objection raised in section 7 on page 4 of the Office Action, wherein previous claims 56 and 57 are objected because the claims recite specific amino acid residues without reciting the sequence of Hsp70 and Bag-4, the Examiner's attention is respectfully directed to the specification of the application as filed, in particular at page 9, lines 24 to 27; at

page 12, lines 20 to 32 and to the Examples, wherein reference to the sequence of specific sequences for Hsp70 and Bag-4 is made. Applicants have further amended the claims to refer to human Hsp70 and Bag-4. Applicants respectfully submit that these sequences are known in the art and thus do not have to be recited in the claims as the person of skill in the art can easily identified the referenced amino acid residues.

4. Claim Rejections - 35 U.S.C § 112, 1st paragraph

Without conceding the correctness of the objections under 35 U.S.C § 112, 1st paragraph at pages 4 to 9 of the Office Action, those objections have been rendered moot in view of the amendments to the claims.

In particular, it has been clarified in claim 1 that the binding domains of the bispecific molecule comprise a first and second antigen binding site as stated by the Examiner in the paragraph bridging pages 6 and 7 of the Office Action.

Furthermore, claim 5 has been clarified in that the first and second immunoglobulin variable region comprises a heavy and light chain variable domain.

Accordingly, it is submitted that the previous basis for rejection of the claims has been overcome and Applicants respectfully request that this rejection be withdrawn.

6. Claim Rejections – 35 USC § 103

In section 12 on pages 9-13 of the Office Action previous claims 1, 8, 15, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gray et al. (US2005/0009033A1), in view of Ozawa et al. (Biochem. Biophy. Res. Commun. 271, (2000), 409-413), Goeddel et al. (US 6,110,690), Multhoff et al. (WO02/22656A2) and Kortt et al. (Biomolecular Engineering 18 (2001), 95-108).

On page 11 of the Office Action, 3rd paragraph, the Examiner states that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to

have made a bispecific antibody that binds to both BAG-4 and Hsp70 in view of Gray and Ozawa.

However, the Examiner´s observations do not apply to the claims as amended.

In particular, in view of the Examiner´s statement in section 1, at page 3 of the Office Action, in that "the instant claims are drawn to a product, per se, the bispecific antibody would inherently bind to membrane Hsp70 and Bag-1" is not correct. In this context, the bispecific molecule of the present invention has been characterized in claim 1 more clearly in that it specifically binds its antigen on viable cells.

The specificity of the bispecific molecule to selectively bind the antigen, i.e. Hsp and Bag on the cell surface can be conferred by using the antigen binding site of the anti-Hsp70 antibody taught in Multhoff and the monoclonal antibodies cmHsp70.1 and cmHsp70.2 deposited with the DSMZ; see the specification at page 12, lines 20 to 28.

As correctly stated by the Examiner at page 11, second paragraph and shown in applicant´s co-pending application WO2005/054925 "Therapeutic and diagnostic anti-Hsp70 antibodies" referred to in the present specification at page 12, lines 28 to 32, antibodies recognizing the carboxyl terminal amino acid residues 454 - 461 of Hsp70 specifically bind Hsp70 on tumor cells because those amino acid residues constitute a particular extracellular localized epitope of Hsp70 which is not visible or formed by Hsp70 intracellularly or in its isolated form.

On the other hand, the person skilled in the art is taught that for example Bag-4 (SODD) exerts its effect intracellularly; see for example Ozawa et al. at page 409, right-hand column, last full sentence stating that Bag-4 specifically binds to intracellular domains of receptor proteins. Consistent to that Goeddel et al. teaches modulating SODD activity within the cell; see Goeddel et al. for example in column 4, lines 24 to 28. Likewise, also other members of the Bag protein family such as Bag-1 are reported to bind to Hsc70 intracellulary, see for example Takayama et

al., e.g. in the abstract. Accordingly, the prior art consistently teaches that the Bag protein is localized in and exerts its effect including binding to Hsp70 or Hsc70 intracellularly.

There is no suggestion or teaching in the prior art that any Bag protein may also be exposed on the cell surface. Likewise, there is no suggestion or teaching in the prior art for a co-localization of Bag and Hsp protein on the cell surface of tumor cells.

Hence, while it might have been *prima facie* obvious to one of ordinary skill in the art – which we deny - at the time the invention was made to have made a bispecific antibody that binds to both Bag-4 and Hsp70 in view of Gray et al. and Ozawa et al., the person skilled in the art had no motivation to use as a first binding domain an antigen binding site which specifically binds Hsp on the cell surface. Rather, the use of a binding domain selectively binding plasma membrane Hsp70 on tumor cells would have been avoided since the person ordinary skilled in the art must have thought that there could be no bispecific binding since the antigen of the second binding domain, i.e. Bag protein resides in the cell. Thus, as already discussed previously, it indeed makes no sense to construct a bispecific molecule comprising one binding domain which specifically binds cells surface membrane bound Hsp protein and a second binding domain which antigen, i.e. Bag protein is localized intracellularly.

In this context, Applicants respectfully submit that the Examiner´s allegation at page 12 of the Office Action that

> "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a bispecific antibody that binds to the carboxyl terminal regions of BAG4 and Hsp70 in view of Ozawa and Multhoff. One would have been motivated to do so because Ozawa et al teach that the 'BAG domain (which is located at the carboxyl terminal region of BAG4) specifically binds and stimulates the ATPase activity of Hsp70/Hsc70 and modulates the function of these molecular chaperones (see page 412, column 2, paragraph 2), and Ozawa et al [sic] teach that the anti-Hsp70 antibody specific to carboxyl terminal region of Hsp70 selectively to plasma

membrane Hsp70 on tumor cells"

is not correct and erroneous. This is because as correctly noted by the Examiner at page 10 of the Office Action Ozawa et al. teach that the Bag domain specifically binds the APTase activity of Hsp70. However, the APTase activity of Hsp70 is located in the amino terminal region of Hsp70; see attached figure as Exhibit A.

Thus, in view of the teaching of Ozawa et al., the person skilled in the art at making a bispecific antibody that binds to Bag-4 and Hsp70 would certainly not use a binding domain for Hsp70, wherein the antigen binding site recognizes the carboxyl terminal regional but the amino terminal region of the protein. Accordingly, the person skilled in the art in following the teaching of the prior art would not arrive at the bispecific molecule as now claimed but to different bispecific molecules which would not be capable of binding cell surface membrane bound Hsp70 and Bag on tumor cells.

For the above reasons, it is submitted that the claims as amended are not obvious over the prior art.

CONCLUSION

It is respectfully submitted that the invention as claimed fully meets all requirements and that the claims are worthy of allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at (608) 662-1277.

Dated: September 8, 2010

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